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Review

Carotid chemoreceptor "resetting" revisited☆

John L. Carroll*, Insook Kim

Division of Pediatric Pulmonary Medicine, Department of Pediatrics, University of Arkansas for Medical Sciences, Arkansas Children's Hospital, 1 Children's Way, Little Rock, AR 72202, United States

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ABSTRACT

Carotid body (CB) chemoreceptors transduce low arterial O_2 tension into increased action potential activity on the carotid sinus nerves, which contributes to resting ventilatory drive, increased ventilatory drive in response to hypoxia, arousal responses to hypoxia during sleep, upper airway muscle activity, blood pressure control and sympathetic tone. Their sensitivity to O_2 is low in the newborn and increases during the days or weeks after birth to reach adult levels. This postnatal functional maturation of the CB O_2 response has been termed "resetting" and it occurs in every mammalian species studied to date. The O_2 environment appears to play a key role; the fetus develops in a low O_2 environment throughout gestation and initiation of CB "resetting" after birth is modulated by the large increase in arterial oxygen tension occurring at birth. Although numerous studies have reported age-related changes in various components of the O_2 transduction cascade, how the O_2 environment shapes normal CB prenatal development and postnatal "resetting" remains unknown. Viewing CB "resetting" as environment-driven (developmental) phenotypic plasticity raises important mechanistic questions that have received little attention. This review examines what is known (and not known) about mechanisms of CB functional maturation, with a focus on the role of the O_2 environment.

1. Introduction

Mammalian life depends on a steady supply of oxygen to tissues to meet cellular metabolic needs, while excess oxygen is highly toxic. Therefore, mammals have developed O_2 sensory systems that operate on multiple levels to optimize cellular O_2 availability and promote tolerance to low O_2 tensions, as well as antioxidant systems to reduce oxygen toxicity. An important generalized oxygen sensing system, operative in every nucleated cell, are the hypoxia-inducible factors (HIF), major regulators of cellular oxygen homeostasis in all metazoan animals. Low oxygen tension increases HIF-1α level, which in turn controls the transcription of hundreds of genes involved in cellular-level adaptations to low oxygen tension (Semenza, 2012; Webb et al., 2009). Other generalized cellular O_2-sensing pathways such as the unfolded protein response, nuclear factor (NF)-kb and the mammalian target of rapamycin (mTOR) promote tolerance to hypoxia by modulating transcription and translation (Dunwoodie, 2009; Gorr et al., 2010). Thus, every nucleated cell in the mammalian body exhibits multiple adaptive responses to hypoxia that aim to minimize the effects of reduced oxygen availability and preserve homeostasis. As tissue O_2 tension depends on oxygen delivery, it is not surprising that mammals have also evolved O_2-regulated control of erythrocyte production, generalized systemic vascular responsiveness to hypoxia and specialized O_2-sensing vascular tissues to regulate blood flow, such as the small pulmonary arteries, fetoplacental arteries and the ductus arteriosus (Semenza, 2011; Waypa and Schumacker, 2010).

In order to ensure optimal oxygen intake, as O_2 needs vary with environment and activity, mammals have developed specialized peripheral arterial chemoreceptor organs that continuously sense arterial blood O_2 tension and directly regulate minute ventilation. The main peripheral arterial O_2 chemoreceptors are the carotid bodies (CB), located bilaterally at the carotid bifurcations. They transduce arterial O_2 levels into action potential activity on carotid sinus nerve afferents, which input via the caudal nucleus tractus solitarii to control minute ventilation and maintain normal Pa_{O_2}, increase ventilatory drive in response to hypoxia, mediate arousal responses to hypoxia during sleep and provide important modulation of upper airway muscle activity, blood pressure and sympathetic tone (Iturriaga et al., 2009; Prabhakar and Kumar, 2010; Sinski et al., 2012). Perhaps surprisingly, given their importance in cardiorespiratory control, the carotid body chemoreceptors are not functionally mature at birth and require time, after birth, to reset their O_2 responsiveness to adult-like levels (Gauda et al., 2009).

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* Corresponding author at: Pediatric Pulmonary Medicine Division, Arkansas Children's Hospital, Mail slot 512-17, 1 Children's Way, Little Rock, AR 72202, United States. Tel.: +1 501 364 1006; fax: +1 501 364 3930.
E-mail address: carrolljohnl@uams.edu (J.L. Carroll).

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A key point, which will be emphasized throughout this review, is that postnatal development of CB oxygen sensitivity depends on the O_2 environment; if Pa_{O_2} is increased before birth onset of resetting can be hastened while, if Pa_{O_2} is kept low after birth, resetting can be delayed (Blanco et al., 1988; Sterni et al., 1999). During development, the oxygen environment changes remarkably, from the very low oxygen intrauterine environment of the embryo during the first 10–11 weeks of gestation, to the moderately hypoxic environment of the 2nd and 3rd trimesters of gestation, to the ~4-fold sudden increase in Pa_{O_2} at birth and the oxygen-rich postnatal environment (Dunwoodie, 2009). The mammalian carotid body forms and undergoes structural maturation in this low O_2 environment. In spite of the low in utero P_{O_2}, CB O_2 responsiveness is low in the fetus and will increase only after exposure to the higher P_{O_2} after birth (Blanco et al., 1984; Eden and Hanson, 1987; Hertzberg and Lagercrantz, 1987). Over the last ~30 years, terminology has evolved describing the carotid chemoreceptors during prenatal development as "set", analogous to a thermostat, to exhibit minimal activity to the normally low Pa_{O_2} (~23–25 mmHg) of the fetus. A logical extension of the "thermostat" analogy is that after birth, when Pa_{O_2} is 4-fold higher compared to fetal Pa_{O_2}, the carotid chemoreceptors "reset" and sense the postnatal Pa_{O_2} of 80–100 mmHg as "normoxia". After "resetting", the range of hypoxia sensitivity shifts such that the Pa_{O_2} of 23–25 mmHg, which elicited minimal CB activity in the fetus, will elicit a brisk increase in carotid sinus nerve activity and would be considered severe hypoxia for an infant.

Although substantial progress has been made in understanding postnatal "resetting" of CB O_2 sensitivity, major questions persist and the fundamental mechanisms underlying dependence on the O_2 environment remain unknown. The goal of this review is to explore further the terminology, concepts, possible mechanisms of "resetting" and the role of the low O_2 environment of the fetus in shaping CB functional development. Although beyond the scope of this review, vascular O_2 sensing, HIF-1, other cellular oxygen-sensing pathways and the effects of altered O_2 environments will be discussed when potentially relevant to CB resetting.

2. CB O_2 transduction – acute hypoxia

Before addressing the question of resetting, it is necessary to consider current views on CB O_2 chemotransduction mechanisms. Carotid body structure is similar across mammalian species, consisting of richly perfused clusters of oxygen-sensitive, neuron-like secretory cells called type-1 or glomus cells, surrounded by glia-like type 2 or sustentacular cells (Fig. 1). The carotid sinus nerve, a branch of cranial nerve IX with cell bodies in the petrosal ganglion (PG), provides the main sensory innervation, forming predominantly afferent synapses on glomus cells (McDonald and Mitchell, 1975). Although not fully proven, it is generally accepted that glomus cells, together with their associated nerve endings and PG cell bodies, comprise a "chemosensory unit", with the glomus cell as the primary site of O_2-sensing, presynaptic to the nerve terminal.

The generally accepted steps in CB O_2 tension transduction, shown in Fig. 1, are as follows (numbers in parentheses correspond to numbered steps in figure): Lowered arterial O_2 tension in CB blood vessels (1) results in lowered tissue oxygen tension and reduced glomus cell intracellular P_{O_2} (2). O_2 sensing within glomus cells occurs at multiple sites, including mitochondria, heme-oxygenase-2 (HO-2) and possibly others. Mitochondrial O_2 sensing (3a), by as yet unknown mechanisms, leads to inhibition of cell membrane resting K^+ current, which is predominantly carried by TASK1/3 (4a) (Kim et al., 2009; Wyatt and Buckler, 2004). Heme-oxygenase-2 (3b), which is tightly associated with cell membrane BK channels (4b), uses O_2 as a substrate to produce carbon monoxide (CO), which enhances BK channel open probability during normoxia (Kemp, 2005). When glomus cell O_2 tension is low, CO production decreases and BK channel activity is suppressed. The inhibition of TASK1/3 current initiates and drives glomus cell depolarization (5), the magnitude of which is increased by the hypoxia-mediated inhibition of BK current (Wasicko et al., 2006). Glomus cell depolarization leads to calcium influx via (6) voltage gated calcium channels and a rapid increase in intracellular calcium levels ($[Ca^{2+}]_i$). (7) The hypoxia-induced increase in $[Ca^{2+}]_i$ leads to release of multiple neurotransmitters contained in secretory vesicles (7a) as well as other transmitters or modulators (7b), such as adenosine, GABA, 5HT and others (see Nurse, 2010 for review). At the glomus cell-CSN nerve terminal synapse, evidence supports ATP, adenosine and ACh as excitatory neurotransmitters (8a) causing depolarization of the nerve endings and (10) generation of spiking activity in the CSN. Other released neuromodulators may have inhibitory or facilitatory actions on the CSN nerve endings (8b) (Nurse, 2010). This wide array of neurochemicals, released by hypoxia into the synaptic cleft and into the space between glomus cells and the enveloping type II cells, also may act on a variety of glomus cell autoreceptors (8c) and, depending on the specific ligand-receptor, either enhance or inhibit the $[Ca^{2+}]_i$ response to hypoxia by a variety of mechanisms (Bairam et al., 2006; Joseph et al., 2006; Nurse, 2010; Shirahata et al., 2007). Additional potentially important steps in O_2 transduction include roles for CSN nerve terminal Na^+ channels and for type II cells. Donnelly has proposed that persistent Na^+ currents in CSN nerve endings (9) may enhance nerve terminal excitability and amplify excitation by neurotransmitters, potentially explaining how a 2–3 fold increase in neurotransmitter release during hypoxia can result in a 20–30 fold increase in single unit CSN activity (Donnelly, 2011). Finally, ATP increases $[Ca^{2+}]_i$ in type II cells and may result in release of additional ATP as a "gliotransmitter" as well as release of other modulators (Tse et al., 2012; Zhang et al., 2012). This has led to a recent surge of interest in the glia-like type II cells as synaptic amplifiers of chemotransduction, similar to the role of glial cells in other neural tissues (Butt, 2011).

The carotid body is often portrayed in a reductionist, highly simplified manner for illustrative purposes, but the reality is potentially complicated. It is important to remember that the transduction mechanisms illustrated in Fig. 1 co-exist in the same cells with multiple other O_2 responsive mechanisms that operate on varying time scales, multiple processes generating reactive oxygen and nitrogen species, multiple anti-toxicity systems to cope with oxidative and nitrosative stress and it is all interwoven within a complicated cellular structure and a reactive (and perhaps interactive) vasculature. In addition, carotid body structural and functional development, with all of its multiple O_2-responsive components, takes place in an O_2 environment that changes markedly over the developmental time span, raising the possibility that the developmental O_2 environment per se is critical in shaping CB development and the subsequent "resetting" that occurs after birth.

3. Carotid body "resetting" revisited

3.1. Terminology – resetting vs. development

The terms "development" and "maturation" encompass changes that occur in CB structure, neurochemistry, physiology and function from its formation in the embryo to full maturity in the adult. In contrast, terms such as "functional development", "functional maturation" refer to age-related changes in specific responses such as the magnitude of the neural response to hypoxia or hypercapnia. These terms can be applied to any time frame during fetal or postnatal development and do not necessarily center on the